Please replace the paragraph on page 3, lines 16-26, with the following paragraph:

One embodiment of the present invention is drawn to compositions comprising photosensitive agents conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; pyrophosphates; thiobisphosphonates; and nitrobisphosphonates. The photosensitizing agent is selected from the group consisting of- indocyanine green (ICG); methylene blue; toluidine blue; aminolevulinic acid (ALA); chlorin compounds; phthalocyanines; porphyrins; purpurins; texaphyrins; and any other agent that absorbs light in a range of 500 nm - 1100 nm. A preferred embodiment of this invention contemplates that the photosensitizing agent is indocyanine green (ICG) and the compound conjugated to ICG is a bisphosphonate. These conjugates may be further conjugated to another ligand where the ligand is a target tissue specific antibody, peptide or polymer.

Please replace the paragraph on page 4, line 23, with the following paragraph:

Figure 2 shows the structure of pyrophosphate.

Please replace the paragraph on page 5, lines 14-22, with the following paragraph:

Terms as used herein are based upon their art recognized meaning and from the present disclosure should be clearly understood by the ordinary skilled artisan. For sake of clarity, terms may also have particular meaning as would be clear from their use in context. For example, transcutaneous more specifically herein refers to the passage of light through unbroken tissue. Where the tissue layer is skin or dermis, transcutaneous includes transdermal and the light source is external to the outer skin layer. Transillumination refers herein to the passage of light through a tissue layer, such as the outer cortex layer of an organ such as bone, where the light source is external to the organ, but internal or implanted into the subject or patient.

Please replace the paragraph on page 7, lines 9-14, with the following paragraph:

"Radiation" as used herein includes all wavelengths. Preferably, the radiation wavelength is selected to match the wavelength(s) or wavebands which excites the photosensitive compound. Even more preferably, the radiation wavelength matches the excitation wavelength of the photosensitive compound and has low absorption by the non-target cells and the rest of the intact animal, including blood proteins. For example, the preferred wavelength for ICG is the range of 750-850 nm.

Please replace the paragraph on page 8, lines 4-10, with the following paragraph:

Preferred photosensitizing agents include, but are not limited to, chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens and pro-drugs such as Δ-aminolevulinic acid, which can produce drugs such as protoporphyrin. More preferred are: methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 500 nm - 1100 nm. Most preferred is indocyanine green (ICG) (for example, see: WO 92/00106 (Raven *et al.*); W097/31582 (Abels *et al.*) and Devoisselle *et al.*, SPIE 2627:100-108, 1995).

Please replace the paragraph on page 8, line 16-25, with the following paragraph:

The bisphosphonate composition also can be conjugated to specific ligands reactive with a target, such as receptor-specific ligands or immunoglobulins or immunospecific portions of immunoglobulins, permitting them to be more concentrated in a desired target cell or microorganism. The photosensitizing agent and/or a bisphosphonate composition may be further conjugated to a ligand-receptor binding pair, which includes, but is not limited to: biotin-streptavidin; chemokinechemokine receptor; growth factor-growth factor receptor; and antigen-antibody. This conjugation may permit lowering of the required dose level since the material is more selectively targeted and less is

wasted in distribution into other tissues whose destruction must be avoided.

Please replace the paragraph on page 8, line 28, through page 9, line 4, with the following paragraph:

The bisphosphonate composition can be administered in a dry formulation, such as pills, capsules, suppositories or patches. The bisphosphonate composition also may be administered in a liquid formulation, either alone with water, or with pharmaceutically acceptable excipients, such as are disclosed in Remington's Pharmaceutical Sciences. The liquid formulation also can be a suspension or an emulsion. Liposomal or lipophilic formulations may be desirable. If suspensions or emulsions are utilized, suitable excipients; include water, saline, dextrose, glycerol, and the like. These compositions may contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, antioxidants, pH buffering agents, and the like.

Please replace the paragraph on page 9, line 25, through page 10, line 4, with the following paragraph:

While not wishing to be limited by a theory, the inventor proposes that a photosensitizer agent can be substantially and selectively photoactivated in the target cells and target tissues within a therapeutically reasonable period of time and without excess toxicity or collateral damage to non-target tissues. Thus, there appears to be a therapeutic window bounded by the photosensitizer agent dosage and radiation dosage. The formation of photodegradation products of a photosensitizer agent was used as an indicator of photoactivation. Photoactivation of a photosensitizer agent has been postulated to cause the formation of singlet oxygen, which has a cytotoxic effect. In view of the problems related to current methods of treating skeletal metastases which are palliative, the envisaged method of targeted transcutaneous PDT of patients injected with a bisphosphonate composition and subjected to a relatively low fluence rate, but high total fluence dose of irradiation is an attractive approach to the treatment of target tissues, that include neoplastic disease and infectious agents.

Please replace the paragraph on page 10, lines 5-20 with the following paragragh:

Additionally, the present invention is drawn to a method for transcutaneous therapy of skeletal metastases in a mammalian subject or patient by first administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target tissue antigen; and simultaneously or subsequently administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to an bisphosphonate composition or bisphosphonate agent delivery system wherein the first member binds to the second member of the ligand-receptor binding pair. These steps are followed by irradiating or sonicating at least a portion of the subject with energy at a wavelength, waveband, or frequency absorbed by said bisphosphonate composition or bisphosphonate agent delivery system, by the product thereof, wherein said energy is provided by an energy source that is external to the subject; and wherein said light irradiation or sonication is at a low dose rate that results in the activation of said bisphosphonate composition or bisphosphonate agent delivery system.

Please replace the paragraph on page 10, lines 21-32, with the following paragraph:

While the preferred embodiment of the present invention is drawn to the use of light energy in a photodynamic therapy of skeletal tumors other forms of energy are within the scope of this invention and understandable by one of ordinary skill in the art. Such forms of energy include, but are not limited to: thermal; ultrasonic; chemical; photo or light; microwave; ionizing, such as: x-ray, and gamma ray; and electrical. For example, sonodynamically induced or activated bisphosphonate compositions include, but are not limited to: gallium-porphyrin complex (see: Yumita *et al., Cancer Letters,* 112: 79-86, 1997); other porphyrin complexes, such as protoporphyrin and hematoporphyrin

(see: Umemura *et al., Ultrasonics Sonochemistry* 3: S187-S191, 1996); other cancer drugs, such as daunorubicin and adriamycin, used in the presence of ultrasound therapy (see: Yumita *et al., Japan J Hyperthermic Oncology,* 3(2): 175-182, 1987).

Please replace the paragraph on page 11, lines 5-21, with the following paragraph:

The ordinary skilled artisan would be familiar with various ligand-receptor binding pairs, including those known and those currently yet to be discovered. Those known, include, but are not limited to the group consisting of: biotin-streptavidin; chemokine-chemokine receptor; growth factor-growth factor receptor; and antigen-antibody. This invention contemplates a preferred embodiment that includes the use of biotin-streptavidin as the ligand-receptor binding pair. However, the ordinary skilled artisan would readily understand from the present disclosure that any ligand-receptor binding pair may be useful provided the ligand-receptor binding pair demonstrate a specificity for the binding by the ligand to the receptor and further provided that the ligand-receptor binding pair permit the creation of a first conjugate comprising a first member of the ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target tissue antigen; and further permit the creation of a second bisphosphonate conjugate comprising a second member of the ligand-receptor binding pair conjugated to a photosensitizing agent or ultrasound sensitive agent, and further wherein the first member binds to the second member of the ligand-receptor binding pair.

Please replace the paragraph on page 11, line 22, through page 12, line 6, with the following paragraph:

A preferred embodiment of the present invention is drawn to a method where the photosensitizing agent delivery system includes a liposome delivery system consisting essentially of the bisphosphonate composition. A still further and preferred embodiment of the present invention contemplates the disclosed

method where the photosensitizing agent delivery system utilizes both a liposome delivery system and a bisphosphonate composition, where each is separately conjugated to a second member of the ligand-receptor binding pair, and where the first member binds to the second member of the ligand-receptor binding pair, and more preferably where the ligand-receptor binding pair is biotin-streptavidin. This embodiment further contemplates that the bisphosphonate composition as well as the photosensitizing agent delivery system may both be specifically targeted through the selective binding to a target tissue antigen by the antibody or antibody fragment of the first member binding pair. Such dual targeting is envisioned to enhance the specificity of uptake and to increase the quantity of uptake. Though the total fluence delivered to the treatment site will be variable depending on the size and nature of the treatment site, it is contemplated that the preferred total fluence delivered either internally or from an external light source will range between 30 Joules to 25,000 Joules, more preferably between 100 Joules to 20,000 Joules, and most preferably between 500 Joules to 10,000 Joules.

Please replace the paragraph on page 12, lines 25-30, with the following paragraph:

The specific dose of bisphosphonate conjugate is that which results in a concentration of active ICG sufficient to obtain a blood level between about 0.001 and 100 μg/ml. and more preferably, a dose of between about 0.01 and 10 μg/ml. However, it is well within the skill of the ordinary skilled artisan to determine the specific therapeutically effective dose using standard clinical practices and procedures.

Please replace the paragraph on page 14, line 25, through page 15, line 2, with the following paragraph:

As Paget's Disease is characterized by abnormally localized enhanced osteoclastic activity followed by abnormal bone formation of poor structural quality, this type of PDT treatment should minimize the bone pain, skeletal deformity, fractures, secondary arthritis, neurologic impairment and hearing loss.

Since increased bone turnover is associated with increased serum levels of alkaline phosphatase and increased urinary excretion of hydroxyproline, deoxypyridinoline and cross-linked N-telopeptide of type I collagen, the efficacy of the treatment may be determined by the serum levels of alkaline phosphatase and/or the urine levels of hydroxyproline, deoxypyridinoline and cross-linked N-telopeptide of type I collagen. Usually, the success of the treatment is estimated by evaluating whether serum alkaline phosphatase has been reduced by 60% or lowered into the normal ranges.

Please replace the paragraph on page 17, line 10-17, with the following paragraph:

Since increased bone turnover is associated with increased serum levels of alkaline phosphatase and increased urinary excretion of hydroxyproline, deoxypyridinoline and cross-linked N-telopeptide of type I collagen, the efficacy of the treatment may be determined by the serum levels of alkaline phosphatase and/or the urine levels of hydroxyproline, deoxypyridinoline and cross-linked N-telopeptide of type I collagen. Usually, the success of the treatment is estimated by evaluating whether serum alkaline phosphatase has been reduced by 60% or lowered into the normal ranges.

In the Claims:

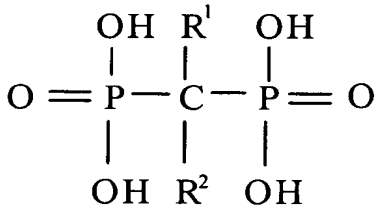
Please replace claims 1-7, 10, 11, 13, 15-20 and 22 with the following claims (a marked-up copy of the amended specification is attached to this Amendment) and please add claims 25-36 as follows:

1. (Amended) A pharmaceutical composition comprising a photosensitizer agent conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; pyrophosphates; thiobisphosphonates; and nitrobisphosphonates.

2. (Amended) The composition of claim 1, wherein the photosensitizer agent is selected from the group consisting of chlorins, bacteriochlorins, phthalocyanines, pórphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, Δ-aminolevulinic acid,

protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 500 nm - 1100 nm.

3. (Amended) The composition of claim 1, wherein the compound is a bisphosphonate of the formula



wherein R^1 is independently selected from the group consisting of: hydroxyl, an amino group, -CN, $-NO_2$, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy; and wherein R^2 is independently selected from the group consisting of: alkyl, aminoalkyl -CN, $-NO_2$, $-NH_2$, haloalkyl, heteroaryl, phenyl, alkyl, al alkylthio, halo and alkyl-carbonyloxy.

4. (Amended) The composition of claim 3, wherein R^1 is hydroxyl or an amino group and R^2 is alkyl or aminoalkyl.

5. (Amended) The composition of claim 3, wherein the compound is selected from the group consisting of etidronate, tiludronate, clodronate, pamidronate, alendronate, risedronate and ibandronate.

6. (Amended) The composition of claim 1, further conjugated to a target tissue specific ligand.

7. (Amended) The composition of claim 1, further conjugated to an imaging agent.

10. (Amended) The method of claim 8, wherein said composition is conjugated to an imaging agent.

11. (Amended) The method of claim 10, further comprising the steps of performing a nuclear medicine scan and imaging the target cells or target tissues to be destroyed or impaired.

13. (Amended) A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising a photosensitizer agent conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; pyrophosphates; thiobisphosphonates; and nitrobisphosphonates, wherein said composition selectively binds the target cells or target tissues involved in said disease of bone tissue; and

irradiating at least a portion of the subject with light at a wavelength absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition, wherein said composition is cleared from non-target tissues of the subject prior to said irradiation.

15. (Amended) A method for treating a metabolic bone disorder or bone metastases in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising

a photosensitizer agent selected from the group consisting of chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, Δ-aminolevulinic acid, protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 500 nm - 1100 nm,

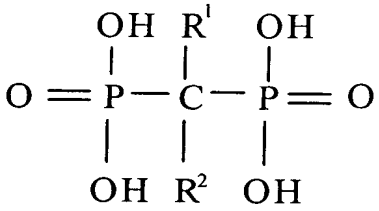
which is conjugated to a compound selected from the group consisting of bisphosphonates; pyrophosphonates; pyrophosphates; thiobisphosphonates; and nitrobisphosphonates which selectively binds the

target tissues or cells involved in the metabolic bone disorder or bone metastases and said composition is further conjugated to an imaging agent; and

performing a nuclear medicine scan;

imaging the target tissues or cells to be treated; and irradiating at least a portion of the subject with light at a wavelength absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition, wherein said composition is cleared from non-target tissues of the subject prior to said irradiation.

16. (Amended) A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject according to claim 13 or 15, wherein said compound is a bisphosphonate of the formula



wherein R^1 is independently selected from the group consisting of: hydroxyl, an amino group, -CN, -NO_2, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy; and wherein R^2 is independently selected from the group consisting of: alkyl, aminoalkyl -CN, -NO_2, -NH_2, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy.

17. (Amended) The method according to claim 16, wherein R^1 is hydroxyl or an amino group and R^2 is alkyl or aminoalkyl.

18. (Amended) The method according to claim 13 or 15, wherein the compound is selected from the group consisting of etidronate, tiludronate, clodronate, pamidronate, alendronate, risedronate and ibandronate.

19. (Amended) The method according to claim 13 or 15, wherein the composition is conjugated to a target tissue specific ligand or an imaging agent.

20. (Amended) A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising a photosensitizer agent, wherein said agent is selected from the group consisting of chlorins, bacteriochlonins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphynin derivatives (BPD), porfimer sodium, Δ-aminolevulinic acid, protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 600 nm -1100 nm, and wherein said agent is conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; pyrophosphates; thiobisphosphonates; and nitrobisphosphonates; and wherein said composition selectively binds the target cells or target tissues involved in said disease of bone tissue; and

irradiating at least a portion of the subject with light at a wavelength absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition; and

wherein said composition is cleared from non-target cells or non-target tissues of the subject prior to said irradiation.

22. (Amended) The method of any one of claims 9-15, 17, 20 and 21, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm^2 to 25,000 Joules/cm^2.

25. (New) The method of claim 8, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm^2 to 25,000 Joules/cm^2.

26. (New) The method of claim 16, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm^2 to 25,000 Joules/cm^2.

27. (New) The method of claim 18, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm^2 to 25,000 Joules/cm^2.

28. (New) The method of claim 19, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm^2 to 25,000 Joules/cm^2.

29. (New) The method of claim 25, wherein said range is between 100 Joules/cm^2 to 20,000 Joules/cm^2.

30. (New) The method of claim 26, wherein said range is between 100 Joules/cm^2 to 20,000 Joules/cm^2.

31. (New) The method of claim 27, wherein said range is between 100 Joules/cm^2 to 20,000 Joules/cm^2.

32. (New) The method of claim 28, wherein said range is between 100 Joules/cm^2 to 20,000 Joules/cm^2.

33. (New) The method of claim 29, wherein said range is between 500 Joules/cm^2 to 10,000 Joules/cm^2.

34. (New) The method of claim 30, wherein said range is between 500 Joules/cm^2 to 10,000 Joules/cm^2.

35. (New) The method of claim 31, wherein said range is between 500 Joules/cm^2 to 10,000 Joules/cm^2.

36. (New) The method of claim 32, wherein said range is between 500 Joules/cm^2 to 10,000 Joules/cm^2.